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(54) THERAPEUTIC AGENT AND METHOD FOR FELINE AIDS VIRUS INFECTIONS AND FELINE ATOPIC DERMATITIS

(57) A therapeutic agent for feline AIDS virus infections, comprising a feline interferon preparation containing a feline interferon as a principal agent (including the treatment of the anemia and chronic stomatitis caused by infection with a feline AIDS virus) and a therapeutic method for feline AIDS virus infections by administering a feline interferon preparation containing a feline interferon as a principal agent to a cat continuously every day are disclosed. Furthermore, a therapeutic method and agent for feline atopic dermatitis are disclosed.

As the feline interferon, an ω feline interferon, particularly a genetically recombinant type ω feline interferon can be preferably used. The ω feline interferon can be an interferon combined with a sugar chain having the amino acid sequence shown in sequence number: 1.

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interferon.

[16] A therapeutic agent for feline atopic dermatitis, according to said [15], wherein the ω feline interferon is a genetically recombinant type interferon.

[17] A therapeutic agent for feline atopic dermatitis, according to said [15] or [16], wherein the ω feline interferon is an interferon combined with a sugar chain having the amino acid sequence shown by sequence number: 1.

[18] A therapeutic method for feline atopic dermatitis, wherein the therapeutic agent for atopic dermatitis stated in any one of said [14] through [17] is injected into a cat.

[19] A therapeutic method for feline atopic dermatitis, according to said [18], wherein the injection is subcutaneous injection.

[20] A therapeutic method for feline atopic dermatitis, according to said [18] or [19], wherein the dose is 0.1 ˜ 5 MU/kg.

The Best Embodiments of the Invention

It is preferable that the feline interferon used in the present invention is an ω feline interferon which can be as produced naturally or can be synthetically synthesized or by any gene recombination technique.

For example, an ω feline interferon produced by a gene recombination technique and marketed under a trade name of " Inter-Cat" (produced by Toray Industries, Inc.) can be used.

The " Inter-Cat" has been approved and practically applied as a therapeutic agent for feline calicivirus infections, and mainly contains an interferon combined with a sugar chain having the sequence of 170 amino acids shown in sequence number: 1, and it is obtained by infecting larvae of Bombyx mori with a recombinant baculovirus, i.e., an insect virus recombined with the gene of an ω feline interferon, and extracting, separating and refining the interferon produced in the bodies of Bombyx mori.

However, the ω feline interferon of the present invention is not necessarily limited to said genetically recombinant type feline interferon.

The ω feline interferons produced by gene manipulation using Escherichia coli, Bacillus subtilis and animal cells such as CHO and also the ω interferon produced from feline cells can also be used. However, in the present situation, the ω feline interferon produced from Bombyx mori is available at low cost.

At first, the therapeutic method for feline AIDS infections is described. The therapeutic method is to inject a therapeutic agent containing an ω feline interferon into a cat once or more per day for 5 or more consecutive days. The dose of the feline interferon is 0.5 MU/kg ˜ 2.5 MU/kg per cat body weight.

It is practical to administer the therapeutic agent once a day. It can be administered once or more per day, but it is preferable to administer at least once a day. It is desirable to administer every day, instead of every other day, and it is more desirable to administer continuously for 5 days or more.

After administering continuously for 5 days or more, the administration can be once suspended, and subsequently continuous administration can be effected again for 5 or more consecutive days.

The dose can also be smaller than 0.5 MU/kg, but if the dose is smaller than 0.5 MU/kg, the therapeutic effect is also weaker. On the contrary, even if the dose is larger than 2.5 MU/kg, the therapeutic cost simply increases, without giving any correspondingly higher effect in most cases.

The injection route can be subcutaneous or intravenous. Intramuscular injection can also be used. However, subcutaneous injection can be practically and simply effected. When the therapeutic method of the present invention was used for treating the anemia as one of feline AIDS virus infections, recovery from impotence and increase of appetite could be achieved, and erythroid values such as erythrocytes, hemoglobin and hematocrit increased.

When used to treat chronic stomatitis, the stomatitis accompanying the ulcers and granulomata of fauces improved and appetite and vitality were restored.

Feline atopic dermatitis is described below. The therapeutic agent for feline atopic dermatitis of the present invention is a preparation containing an ω feline interferon as a principal agent, and when it is used, a solution obtained by dissolving it into physiologic salt solution or infusion solution or any other solution is injected. The injection route can be subcutaneous, intravenous or intramuscular. Subcutaneous injection is preferably simple and practical. The number of administration times is not especially limited, but it is practical to administer once a day every day or 1 to 3 times per week. The dose is not limited either, but is usually 0.1 to 5 MU/kg. A preferable range is 1 to 2.5 MU/kg. The administration effect can be clearly observed from about the 2nd week in most cases.

The ω feline interferons usually do not cause remarkable fever after administration unlike human beings, and even if fever occurs, the body temperature rise as slight as about 1°C only occurs for a while. Serious side effects such as vomition and diarrhea are not caused.

Examples

The present invention is described below in reference to examples, but is not limited thereto or thereby. The blood cell count is in number per microliter (/μl).

[Example 1]

A genetically recombinant type ω feline interferon preparation (trade name: Inter-Cat) was administered to a Japanese cat (female) of 3 to 4 years old who had been suffering the anemia caused by infection with a feline AIDS virus. On the day of the first medical examination, the body weight was 3.7 kg, and she had lost appetite from the previous day, remained impotent and showed pale mucous membranes.

Tetracycline was subcutaneously injected by 1.85 ml, and a vitamin preparation was subcutaneously dripped by 500 ml. On the following day, the body weight became 4.0 kg. In a virus test, she was positive in anti-FIV antibody and negative in FeLV antigen. Blood test values were WBC 12600, erythrocytes 144,000, hemoglobin 3.7 g/dl, hematocrit 12.3%, mean cell volume (MCV) 85 fl, mean cell hemoglobin concentration (MCHC) 30.1 g/dl and thrombocytes 163,000.

Inter-Cat was dissolved into physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 10 MU/day for 3 days. The dose per body weight was 2.5 MU/kg. An infusion solution (vitamin preparation) was subcutaneously dripped by 500 ml/day, and an antibiotic (tetracycline) was subcutaneously injected by 1.85 ml.

From the 4th day, Inter-Cat was decreased to 4 MU/day, and subcutaneously injected for 4 days. The dose per body weight was 0.75 MU/kg.

On the 5th day, appetite was restored a little.

On the 8th day, blood test values were WBC 10400, erythrocytes 358, hemoglobin 4.9 g/dl, hematocrit 28.5%, mean cell volume (MCV) 65 fl, mean cell hemoglobin concentration (MCHC) 30.2 g/dl and thrombocytes 178,000. The body weight was 3.4 kg.

Still after the 85th day, vitality and appetite remained normal. The blood test values were WBC 11400, erythrocytes 971, hemoglobin 11.8 g/dl, hematocrit 40.3%, mean cell volume (MCV) 42 fl, mean cell hemoglobin concentration (MCHC) 29.3 g/dl and thrombocytes 198,000. The body weight was 3.9 kg.

[Example 2]

A genetically recombinant type ω feline interferon preparation (trade name: Inter-Cat) was administered to a Japanese cat (male) of 6 to 7 years old who had been suffering the anemia caused by infection with a feline AIDS virus. On the day of the first medical examination, the body weight was 7.55 kg. Appetite had declined from the previous day, and he was impotent.

In a virus test, he was positive in anti-FIV antibody and negative in FeLV antigen. An anti-inflammatory drug, loxoprofen sodium was administered by 1/2 tablet twice a day.

The cell test values were WBC 3500, erythrocytes 3,670,000, hemoglobin 5.3 g/dl, hematocrit 18.4%, mean cell volume (MCV) 50 fl, mean cell hemoglobin concentration (MCHC) 31.5 g/dl and thrombocytes 105,000.

Inter-Cat was dissolved into physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 10 MU/day for 3 days. On the 4th day, the dose was decreased to 2.5 MU/day, and the Inter-Cat solution was subcutaneously injected for further 3 days. From the 7th day, the dose was increased to 10 MU/day, and the Inter-Cat solution was subcutaneously injected for 3 days.

On the 9th day, the blood test values were WBC 10600, erythrocytes 4,020,000, hemoglobin 6.4 g/dl, hematocrit 21.0%, mean cell volume (MCV) 52 fl, mean cell hemoglobin concentration (MCHC) 30.5 g/dl and thrombocytes 351,000. Appetite was restored a little. The body weight was 7.3 kg.

On the 18th day, he came to hospital again due to anorexia. The body weight was 7.05 kg. The blood test values were WBC 6900, erythrocytes 10,430,000, hemoglobin 16.0 g/dl, hematocrit 51.7%, mean cell volume (MCV) 50 fl, mean cell hemoglobin concentration (MCHC) 30.9 g/dl and thrombocytes 324,000.

Inter-Cat was subcutaneously injected by 10 MU/day for 7 days. An antibiotic (Bitoryl) was administered by 1/2 tablet twice a day. Infusion was effected on the 18th day only. Still after one month, vitality and appetite remained recovered.

[Example 3]

A genetically recombinant type ω feline interferon preparation (trade name: Inter-Cat) was administered to a 10-year-old Japanese cat (male) who had been suffering the chronic stomatitis caused by infection with a feline AIDS virus. On the day of the first medical examination, the body weight was 4.6 kg, and saliva and the ulcers and granulomata of

fauces on both sides were observed. In a virus test, he was positive in anti-FIV antibody and negative in FeLV antigen.

Inter-Cat was dissolved in physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 10 MU/day for 3 days. The dose per body weight was 2.17 MU/kg. After the 4th day, the dose was decreased to 4 MU/day, and the Inter-Cat solution was subcutaneously injected for further 4 days. Only on the 2nd day, an infusion solution (vitamin preparation) was subcutaneously dripped by 500 ml. An antibiotic (Bitoryl) was administered every day.

On the 3rd day, appetite was restored a little. Saliva was also improved a little. As for the stomatitis, the granuloma on the left side became slightly less reddish.

On the 4th day, as for the stomatitis, the granuloma on the left side was reduced in size and reddishness.

On the 5th day, as for the stomatitis, the granuloma on the right side vanished, and the granuloma on the left side was further reduced in reddishness.

On the 7th day, appetite was restored, and as for the stomatitis, ulcers and granulomata vanished. On the 10th day, the body weight was 4.95 kg.

Still after six months, the stomatitis was not worsened.

[Example 4]

A genetically recombinant type ω feline interferon preparation (trade name; Inter-Cat) was administered to an 8-year-old Japanese cat (male) who had been suffering the chronic stomatitis caused by infection with a feline AIDS virus. On the day of the first medical examination, the body weight was 3.4 kg, and saliva and ulcers and granulomata of fauces on both sides were observed. In a virus test, he was positive in anti-FIV antibody and negative in FeLV antigen.

Inter-Cat was dissolved into physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 8.5 MU/day for 7 days. The dose per body weight was 2.5 MU/kg.

After the 8th day, the dose was decreased to 4 MU/day, and the Inter-Cat solution was subcutaneously injected for further 4 days. On the 2nd day only, an infusion solution (vitamin preparation) was subcutaneously dripped by 300 ml. Antibiotics (Dalacin; clindamycin) were administered every day.

On the 7th day, appetite was restored. The body weight was 3.75 kg. Saliva improved, and the stomatitis also improved.

After two months, the stomatitis was not especially worsened, but Inter-Cat was subcutaneously injected by 2.5 MU/kg for 7 days.

After further six months, the stomatitis was not worsened.

[Example 5]

A 4-year-old unsexed female house cat (short hair, Japanese cat) (white, body weight 2.62 kg) came to hospital for the main reason that red eczema occurred in the abdominal part since several days before, and was diagnosed to suffer atopic dermatitis. A preparation containing a ω feline interferon (recombinant type) as a principal agent, i.e., " Inter-Cat" was dissolved into physiological solution, and the Inter-Cat solution was subcutaneously injected by 5 MU/head (1.9 MU/kg). The administration of " Inter-Cat" was continued at intervals of twice a week, and after 8 weeks, the eczema perfectly vanished.

[Example 6]

A 3-year-old female house cat (Cornish Rex) (white, body weight 2.76 kg) had eosinophilic plaques formed with the renal skin thickened since several months before, and was cured temporarily by periodical administration of a steroid hormone preparation. However, after a while, many plaques occurred on the face and the back. In the regions around the ears, portions considered to show the generation of a fungus existed. The disease was diagnoised as atopic dermatitis. A preparation containing a ω feline interferon (recombinant type) as a principal agent, i.e., " Inter-Cat" was dissolved into physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 5 MU/head (1.81 MU/kg). An antihistaminic agent used since before was also used together. The administration of " Inter-Cat" was continued at intervals of once a week. From the 2nd week, the reddishness of the eczema began to vanish, and after 3 months, only a trace remained to show almost perfect healing.

[Example 7]

A 6-year-old unsexed female house cat (short hair, Japanese cat) (blackish tiger color, body weight 4.55 kg) had had miliary eczema on the back due to flea allergy since two years before, and the administration of a steroid hormone preparation and thorough flea extermination could bring about a lesion. However, since about one year before, many eosinophilic plaques were formed in the abdominal part, and though the administration of the steroid hormone prepa-

[Sequence table]

Sequence number: 1

Length of sequence: 170

Type of sequence: Amino acids

Sequence

Cys Asp Leu Pro Gln Thr His Gly Leu Leu Asn Arg Arg Ala Leu Thr
5 10 15

Leu Leu Gly Gln Met Arg Arg Leu Pro Ala Ser Ser Cys Gln Lys Asp
20 25 30

Arg Asn Asp Phe Ala Phe Pro Gln Asp Val Phe Gly Gly Asp Gln Ser
35 40 45

His Lys Ala Gln Ala Leu Ser Val Val His Val Thr Asp Gln Lyn Ile
50 55 60

Phe His Phe Phe Cys Thr Glu Ala Ser Ser Ser Ala Ala Trp Asn Thr
65 70 75 80

Thr Leu Leu Glu Glu Phe Cys Thr Gly Leu Asp Arg Gln Leu Thr Arg
85 90 95

Leu Glu Ala Cys Val Leu Gln Glu Val Glu Glu Gly Glu Ala Pro Leu
100 105 110

Thr Asn Glu Asp Ile His Pro Glu Asp Ser Ile Leu Arg Asn Tyr Phe
115 120 125

Gln Arg Leu Ser Leu Tyr Leu Glu Glu Lys Lys Tyr Ser Pro Cys Ala
130 135 140

Trp Glu Ile Val Arg Ala Glu Ile Met Arg Ser Leu Tyr Tyr Ser Ser
145 150 155 160

Thr Ala Leu Gln Lys Arg Leu Arg Ser Glu
165 170

ration showed reaction, the effect gradually diminished. The disease was diagnosed as atopic dermatitis. A preparation containing an ω feline interferon (recombinant type) as a principal agent, i.e., " Inter-Cat" was dissolved into physiological salt solution, and the Inter-Cat solution was subcutaneously injected by 5 MU/head (1.1 MU/kg). The administration of " Inter-Cat" continued at intervals of once a week. After 2 weeks, reddishness almost vanished, and still after 2 months, the disease did not recur.

Industrial Applicability

The present invention is an effective therapeutic agent containing an ω feline AIDS virus, for treating the anemia and chronic stomatitis caused by infection with a feline AIDS virus, confirmed by a virus test of feline blood because of being positive in anti-feline AIDS virus antibody (anti-FIV antibody), and also is an effective therapeutic method using said therapeutic agent. Furthermore, the therapeutic agent containing an ω feline interferon is a new excellent therapeutic agent and method for feline atopic dermatitis. The present invention is highly industrially useful.

Claims

1. A therapeutic agent for feline AIDS virus infections, comprising a feline interferon preparation containing a feline interferon as a principal agent.

2. A therapeutic agent for feline AIDS virus infections, according to claim 1, wherein the feline interferon is an ω feline interferon.

3. A therapeutic agent for feline AIDS virus infections, according to claim 2, wherein the ω feline interferon is a genetically recombinant type interferon.

4. A therapeutic agent for feline AIDS virus infections, according to claim 3, wherein the ω feline interferon is an interferon combined with a sugar chain having the amino acid sequence shown in sequence number: 1.

5. A therapeutic agent for feline AIDS virus infections, according to any one of claims 1 through 4, which is used for treating the anemia caused by infection with a feline AIDS virus.

6. A therapeutic agent for feline AIDS virus infections, according to any one of claims 1 through 4, which is used for treating the chronic stomatitis caused by infection with a feline AIDS virus.

7. A therapeutic method for feline AIDS virus infections, comprising the step of administering a feline interferon preparation containing a feline interferon as a principal agent to a cat every day.

8. A therapeutic method for feline AIDS virus infections, according to claim 7, wherein the feline interferon is an ω feline interferon.

9. A therapeutic method for feline AIDS virus infections, according to claim 8, wherein the ω feline interferon is a genetically recombinant type interferon.

10. A therapeutic method for feline AIDS virus infections, according to claim 9, wherein the ω feline interferon is an interferon combined with a sugar chain having the amino acid sequence shown in sequence number: 1.

11. A therapeutic method for feline AIDS virus infections, according to any one of claims 7 through 10, which is used for treating the anemia caused by infection with a feline AIDS virus.

12. A therapeutic method for feline AIDS virus infections, according to any one of claims 7 through 10, which is used for treating the chronic stomatitis caused by infection with a feline AIDS virus.

13. A therapeutic method for feline AIDS virus infections, according to any one of claims 7 through 12, wherein the ω feline interferon is administered by a dose of 0.5 MU/kg ~ 2.5 MU/kg per cat body weight once or more per day for 5 or more consecutive days.

14. A therapeutic agent for feline atopic dermatitis, comprising a feline interferon.

15. A therapeutic agent for feline atopic dermatitis, according to claim 14, wherein the feline interferon is an ω feline interferon.

16. A therapeutic agent for feline atopic dermatitis, according to claim 15, wherein the ω feline interferon is a genetically recombinant type interferon.

17. A therapeutic agent for feline atopic dermatitis, according to claim 15 or 16, wherein the ω feline interferon is an interferon combined with a sugar chain having the amino acid sequence shown by sequence number: 1.

18. A therapeutic method for feline atopic dermatitis, wherein the therapeutic agent for atopic dermatitis stated in any one of claims 14 through 17 is injected into a cat.

19. A therapeutic method for feline atopic dermatitis, according to claim 18, wherein the injection is subcutaneous injection.

20. A therapeutic method for feline atopic dermatitis, according to claim 18 or 19, wherein the dose is 0.1 ~ 5 MU/kg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/03963

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K38/21, C07K14/555, C12P21/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K38/21, C07K14/555, C12P21/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Program and Abstracts "2nd National Conference" (Human Retroviruses and Related Infections) (sponsored by The American Society for Microbiology in collaboration with NIH and CDC (29. Jan. 1995 - 2. Feb. 1995), P. 149, Session 74, 512	1-4, 7-10, 13
P	JP, 9-40580, A (Boehringer Ingelheim Int. GmbH.), February 10, 1997 (10. 02. 97)(Family: none)	1 - 17
Y	JP, 6-340549, A (Hayashibara Biochemical Laboratories, Inc.), December 13, 1994 (13. 12. 94) & EP, 619120, A	1 - 12
X Y	JP, 3-15390, A (Toray Industries, Inc.), January 23, 1991 (23. 01. 91), Page 7, lower left column to lower right column (Family: none)	6, 12 1, 5-7, 11, 12

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
February 9, 1998 (09. 02. 98)	February 24, 1998 (24. 02. 98)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/03963

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 2-195884, A (Toray Industries, Inc.), August 2, 1990 (02. 08. 90) & EP, 322870, A & US, 5508291, A	1, 5-7, 11, 12
Y	J. Vet. Med. Sci., Vol. 55, No. 2 (1993) P. 251-258, particularly Fig. 10	1-4, 7-10, 13
X	Immunogenetics, Vol. 42, No. 5 (1995) P. 440-441, particularly page 441, left column, lines 27 to 32	6, 12
Y	J. Virol., Vol. 64, No. 4 (1990) P. 1429-36, particularly page 1429, left column, line 3	5, 11
Y	J. Acquired Immune Defic. Syndr., Vol. 3, No. 8 (1990) P. 787-796	1, 5-7, 11, 12
A	JP, 6-48957, A (Toray Industries, Inc.), February 22, 1994 (22. 02. 94) & WO, 95/20395, A & EP, 694307, A	14 - 20
PX	WO, 96/3435, A (Biotech Limited, UK), February 8, 1996 (08. 02. 96) & AU, 9530831, A	6, 12
Y	Antiviral Res., Vol. 11, No. 3 (1989) P. 147-160	1, 5-7, 11, 12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/03963

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The inventions of claims 14 to 17 and 18 to 20 relate to the therapy of atopic dermatitis by using a feline interferon.

On the other hand, the invention of claim 1 relates to the therapy of feline AIDS virus infections by using a feline interferon.

Since it cannot be considered from the description of the application that there is any relevancy between the pharmacological activity in the treatment for the feline atopic dermatitis and the pharmacological activity in the treatment for feline AIDS virus infections, these groups of inventions cannot be said to be a group of inventions so linked as to form a single general inventive concept.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)